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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/720,603	CHAKRABARTY ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *11-19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *attached is a notice to comply*.

Response to Arguments and Amendments

The Amendment filed on 2/23/07 in response to the previous Non-Final Office Action (11/24/06) is acknowledged and has been entered.

Claims 1-2 have been amended. Claims 1-21 are pending. Claims 11-19 and 21 have been previously withdrawn for non-elected invention. Claims 1-10 and 20 are under consideration.

The following office action contains NEW GROUNDS of rejection.

Priority

It is noted that claims 1, 2, 9 and 10 and their dependent claims have effective priority date of 8/15/2003 as stated in the previous office action dated 11/24/06. The office also establishes effective filing date of 8/15/2003 for claims 8 and 20 in view of an intervened reference applied in this office action.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. The disclosure contains sequences that need SEQ ID numbers for figure 11. If these sequences are found in the sequence listing filed 11/24/2003, applicants need only insert the appropriate SEQ ID Nos. However, if these sequences are not part of the listing, then applicants need to comply with the sequence rules. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply (see attached form, PTO L90).

Rejections Withdrawn

1. The rejection of claims 1-6 under 35 USC § 102(a) being anticipated by Zabonina et la is withdrawn in view of the amendments to the claims to "administering to a patient".

Response to Arguments

1. Rejection under 35 U.S.C. 112 second paragraph

Claims 1-10 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated below.

The following is a quotation of the **second paragraph** of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

> Claims 1-10 and 20 are indefinite because the term "an effective amount" in claim 1 is not clear. MPEP2173.05 state:
> *The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954).*
>
> The specification does not indicated what " an effective amount " is. The specification, although provide a teaching for treating a disease condition or a cell with variant amounts of azurin, does not teach what the effective amount is in the method. For example, figure 12-b show 100ug/ml wild type (wt) azurin has cytotoxicity to more than 50% of the cells, while in figure 14, the same amount of wt azurin has only 20% of cytotoxicity to the cells. Thus, one skilled in the art could not determine what "an effective amount" is. Therefore, the metes and bounds of "an effective amount" in claim 1 cannot be determined, Claim 1 renders the dependent claims indefinite.

The response filed 2/23/07 has been carefully considered but is deemed not to be persuasive. The response states that the function to be rendered effective in the present invention is clearly stated in the claim: "*administering to a patient an effective amount of a cupredoxin to promote cell death*". Applicant then argues on page 6 that *one skilled in the art would expect azurin to effect variant levels of cytotoxicity depending on the types of cell targeted and know 100ug/ml azurin is effectively cytotoxic against over 50% of macrophage and 400ug/ml to 40% melanoma*. In response to this argument, first, the amended claims are drawn to administering amount of cupredoxin to a patient, while the example and figures teach the cytotoxicity to cells in an in vitro cytotoxicity assay, one skilled in the art can not easily convert to an effective amount for in vivo patient treatment from the cytotoxic effect amount of in vitro assay result. Secondly, claimed invention is involved in using the method of cupredoxin for treating a patient. Cupredoxin comprise many species, while the disclosure only provides cytotoxic data of azurin, which could be significantly different from the other species such as plastocyanin being used for the

patient treatment. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained as reason of the records.

2. Rejection under 35 USC § 112 first paragraph

Written description:

Claims 1-10 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement stated again as below.

The following is a quotation of the **first paragraph** of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of treating a condition related to resistant to cell death comprising administering an effective amount of a cupredoxin comprising azurin and plastocyanin, variant or derivative thereof to promote cell death, wherein the cupredoxin binds to p53. The claims further recite the azurin comprising the amino acid SEQ ID NO: 1 or at least 90% identity to SEQ ID NO: 1 and plastocyanin comprising amino acid SEQ ID NO: 2 or at least 90% identity to SEQ ID NO: 2. Thus, the claims are including using a genus of variants, derivatives of azurin and plastocyanin to treat a condition related to resistant to cell death.

The specification teaches a method of inducing breast cancer cell death by wild type azurin and plastocyanin (examples 21-22 and 23). The specification teaches an animal model established with melanoma tumors, which is treated with azurin (figure 6 and 8). The specification also describes mutants of azurin with a few amino acid substitutions (figure 11) and the their cytotoxicity to macrophage (figure 12). However, the specification does not teach **1)** a method of treating resistant cells with mutants or variants of plastocyanin comprising the polypeptide at least 90% identity to SEQ ID NO: 2; **2)** a method of administering any plastocyanin and azurin comprising mutants or any mutants of variants of azurin having at least 90% identity to SEQ ID NO: 1 to a subject with melanoma tumor; **3)** either plastocyanin or azurin or their mutants or variants binds to p53 in the process of inducing cell death or cytotoxicity.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristic, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613".

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d ,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information in the claimed method of

treating a disease condition with variants, derivatives of azurin and plastocyanin. The specification does not provide a specific or detail structural characteristics of the variants or derivatives having 90% identity to azurin or plastocyanin of SEQ ID NO:1 or 2 used in the method. Thus, one of skill in the art would reasonably conclude that the inventor(s), at the time the application was filed, **did not have** possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) and functional attribute(s) of the encompassed genus of variants or derivatives of azurin and plastocyanin used in the method, and therefore conception is not achieved until **reduction to practice has occurred**, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of treating a condition related to resistance to cell death comprising administering azurin consisting of SEQ ID NO: 1, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The response filed 2/23/07 has been carefully considered but is deemed not to be persuasive. Applicant, on page 7 paragraph 2, argues that the specification disclose that plastocyanin like azurin, is cupredoxin, and that plastocyanin has SEQ ID NO: 2 and azurin has sequence of SEQ ID NO:1 and further argue that specification teaches plastocyanin is cytotoxic factor and administration of plastocyanin. In response to this argument, applicant is noted that the underlined paragraph above emphasizes the Office's position and again the specification disclose 1), in vitro method of inducing breast cancer cell death by both wild type of azurin and plastocyanin; 2) in vivo method of treating tumor with only azurin; 3) in vitro method of inducing cytotoxicity to macrophage by wild type and a few mutants of azurin. However, claimed invention are drawn to in vivo treating a patient with cupredoxin and a variant or derivative thereof, the specification does not disclose claimed invention of using variant or derivatives of cupredoxin or any polypeptide having 90% identity to SEQ ID NO:1 and 2 in the method above and not disclose any mutant of plastocyanin binding to p53 in the process of inducing cell death or cytotoxicity during the treatment.

The response, on bridge page 7-8, states that *no claims are made herein to the administration of plastocyanin comprising mutant azurin*. Applicant's request for clarification for the sentence stating

"administering any plastocyanin comprising mutants or any mutants of variant of azurin having at least 90% identity to SEQ ID NO:1". The examiner is clarifying that the sentence means the administering any plastocyanin (including wild type and variant) and mutants or variants of azurin having at least 90% identity to SEQ ID NO: 1 to a patient. The office apologizes for the oversight. In response to this argument, again, the base claim 1, as written originally and amended, claims a method of treating a condition.... comprising administrating..... cupredoxin, or variant, derivative thereof. Since the species azurin and plastocyanin are elected for examination currently, the mutants or variants of azurin and plastocyanin are considered to be the variant or derivative of cupredoxin. The specification actually does not teach in vivo administering a patient with any mutant or variant of any species of cupredoxin including azurin and plastocyanin.

The response, page 8, paragraphs 1-3, states that *claim 1 and 2 have been amended to administration a patient ... function variant or derivative thereof and the specification supports the claims by teaching the creation of variant factor retaining cytotoxic function... retaining toxicity etc. on page 31 and how to create functional variants on page 47 and test the functional variant on example 20 and figure 12(b).* In response to this, again, the specification, although, teaches all stated above, the specification does NOT teach the claimed invention, that is, administering the variants or derivative of cupredoxin to a patient to treat a condition. Thus, one skilled in the art would not be convinced that applicant had the possession of the claimed method.

Applicant, page 8, paragraph 4, further argue that *the specification does teach binding cupredoxin or its functional variant p53 by incorporation of reference by Yamada et al., and mutant azurin exhibiting cytotoxic activity depending on whether their continued ability of the mutant to form p53 complexes.* In response to this argument, as described by Yamada et al., induction cell death by azurin may be due to the p53 binding. Although the figure 12 teaches a few mutants with a few amino acid substations having cytotoxicity to the macrophage as the wild type azurin, the specification does not teach all the variants or derivatives having 90% sequence identity to SEQ ID NO:1 could bind to p53 and induce cell death. The figure 12 has confirmed that not all the variants or derivatives having cytotoxicity to the macrophage as the wild type azurin, such as M44KM64E mutant. Again, no experimentation or working example showing

the activity of variants or derivatives having 90% sequence identity to SEQ ID NO: 2 are administered to a patient in vivo in the specification.

Applicant further argues that *chemical structure of genus of variants of azurin and plastocyanin stating that claim 1 as amended is directed to functional variants described in example 19 and figure 11.* In response to this argument, the claim 1 is broadly drawn to any functional variant of cupredoxin in treating a patient, while figure 1 and example 19 only teach the structure of a few variants of one species azurin, NOT teach A) the structure of any variant of any other species comprising elected plastocyanin or other species, B) the treating a patient in vivo by administering the variants comprising the variants of azurin stated above. Thus, one skilled in the art would not be convinced that applicant had the possession of the claimed method.

In summary, the specification only provide in vivo method of treating a patient with wild type of azurin (SEQ ID NO:1), not other species of cupredoxin, not the variants or derivative of any cupredoxin comprising azurin and plastocyanin. Therefore, one skilled in the art would not be convinced that applicant had the possession of the claimed method of in vivo treating a patient with a cupredoxin, or a derivative thereof. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained as reasons of the record.

Enablement

Claims 1-10 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement stated again as below.

> The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands*, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)
>
> The claims are broadly drawn to a method of treating a condition related to resistant to cell death comprising administering an effective amount of a cupredoxin comprising azurin and plastocyanin, variant or derivative thereof to promote cell death, wherein the cupredoxin binds to p53. The claims further recite the azurin comprising the amino acid SEQ ID NO: 1 or at least 90% identity to SEQ ID NO:1 and plastocyanin comprising amino acid SEQ ID NO: 2 or at least 90% identity to SEQ ID NO: 2.
>
> The specification teaches a method of inducing breast cancer cell death by wild type azurin and plastocyanin (examples 21-22 and 23). The specification teaches an animal model established with melanoma tumors, which is treated with azurin (figure 6 and 8). The specification also describes mutants of azurin with a few amino acid substitutions (figure 11) and the their cytotoxicity to macrophage (figure 12).

However, the specification does not teach **1)** a method of treating resistant cells with mutants or variants of plastocyanin comprising the polypeptide at least 90% identity to SEQ ID NO: 2; **2)** a method of administering any plastocyanin comprising mutants or any mutants of variants of azurin having at least 90% identity to SEQ ID NO: 1 to a subject with melanoma tumor; **3)** either plastocyanin or azurin or their mutants or variants binds to p53 in the process of inducing cell death or cytotoxicity. In addition, the specification on page 50-51, example 20-21 and figure 12-13, teaches that the mutants of azurin, M44KM64E (SEQ ID NO: 7), C112D (SEQ ID NO: 6), or S3S5 etc. do not have cytotoxicity to the cells and no apoptosis induction with these mutants, which does teach away from the claimed method of treating cell to promote cell death by administering the mutants or variants of azurin or plastocyanin. Thus, the specification fails to provide objective evidence, which enable the claimed method of treating a condition related to resistant to cell death comprising administering a variant or derivative of azurin or plastocyanin. The specification also fails to provide objective evidence, which azurin or plastocyanin or variants, derivative binds to p53 to promote the cell death.

It is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). It is also know in the art that even a single modification or substitution in a protein sequence can alter the protein function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al, Journal of Cell biology, Vol 111, p2129-2138, 1990). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz et al., Proc Natl Acad Sci USA, vol 84, p6408-6411, 1987). Removal of the amino terminal histidine of glucagons substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin et al Biochemistry USA, vol 14, p1559-1563, 1975). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

The claims are broadly drawn to a method of treating a condition related to resistant to cell death comprising administering an effective amount of a azurin and plastocyanin, or variant or derivative thereof comprising amino acid having at least 90% identity to SEQ ID NO: 1 or 2. Since the specification does not provide claimed method as discussed above, one skilled in the art would not know how to use the claimed method on the basis of teachings in the prior art or instant specification.

In view of the lack of guidance, lack of examples, and lack of predictability associated claimed method of treating a condition related with cell death by administering azurin, or plastocyanin, or variant, or derivative thereof to promote cell death in a cell, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention.

Applicant states that *claim 1 has been amended to "administering to a patient a cupredoxin or a functional variant or derivative thereof to promote cell death and again point out page 31 of specification having the support for the functional variant retaining the cytotoxicity function (page 10-11) and also indicating the working example for azurin mutants provided in page 47, 50, figure 12 etc.* In response to this argument, the claims, although amend to ...functional variant..... the specification does not provide any teaching using "functional variant" in the claimed method, e. g. administering the functional variant. The argument above provides an in vitro method of using variants of azurin, not in vivo treating a patient. One skilled in the art would understand that in vitro assay some of the variants having cytotoxicity to macrophage as described in figure 12 would not guarantee that administering a patient with such variants

work for treating a condition by promoting cell death, undo experimentation would be forced before practice the claimed invention. In addition, the binding to p53 by the variants has been discussed above.

Applicant further argues that the *cytotoxic function of variants of azurin comprising SEQ ID NO: 7 and 6 or S3S5 to macrophage have been shown in figure 12 and some of the variants, such as C112 D has pronounce apoptotic activity*. The Office agrees with applicant, figure 12 and 13 have shown the apoptosis rate and cytotoxicity induced by some of, not all the variants in vitro, especially C112D. However, the specification neither shows the example for a correlation between in vitro function and in vivo treatment using those variants, nor the direction or guideline how to use these variants for treating a patients based on the in vitro result. Because the result of in vitro treatment is unpredictable, undo experimentation must be required before one skilled in the art could practice claimed invention.

Applicant further argues that *M44KM64E does not have function in cytotoxicity and induction apoptosis activity, but show significant inhibition of cell cycle, for this reason, M44KM64E would be desirable as a variant of cupredoxin useful in promoting cell death progression* (page 13, para 1). In response to this argument, one skilled in the art know that function of cytotoxicity is lysing cells, apoptosis is programmed cell death by DNA fragmentation, and inhibition of cell cycle progression is arresting cells at different cell cycle stage, which are all involved in different mechanisms, steps and proteins expressed in the cells. Claimed invention is drawn to a method of treating a patient with a functional variant of cupredoxin to promote cell death. While M44KM64E shows significant inhibition of cell cycle, which is not necessary to induce cell to die or promote cell death because the cell cycle inhibition could be reversed or overcome at certain condition. Therefore, the variant of cupredoxin, M44KM64E, is obviously not a candidate functional variant used for the claimed invention. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for reasons of the records.

3. Rejection under *Double Patenting*

The rejection of claims 1, 3, and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18, 20, 21 of copending Application No. 11435592 is maintained for the reasons of record in the prior Office Action (11/24/06, page 9). Applicant states that a

terminal disclaimer will be filed if warranted by the examiner's rejection in view of the allowed claims. The office will hold this provisional rejection in abeyance until there is allowable subject matter in the present application as below.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 1,3, and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18, 20, and 21 of copending Application No.11435592 (592') and 19-22 of copending Application No.11488693 (693'). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1, 3, and 20 of instant application are drawn to a method of treating a condition related to resistant to cell death comprising administering an effective amount of a cupredoxin, or variant or derivative thereof, wherein resistance to cell death is human melanoma.

Claims 18 and 20-21 of 592' are drawn to a method of treating patient suffering cancer comprising administering to a patient with a therapeutically effective amount of a cupredoxin, wherein cancer is melanoma.

Claims 19-22 of 693' are drawn to method of treating patient suffering angiogenesis comprising administering to a patient with a therapeutically effective amount of a cupredoxin, wherein suffering is melanoma.

The claims in the instant application and claims in applications of 592' and 693' are directed to a method of treating patient suffering melanoma related disease comprising administering to a patient with a therapeutically effective amount of a cupredoxin. The only difference among the claim sets is cancer related disease is resistant to cell death in the instant application, cancer in the 592' and angiogenesis in the 693', which all are related with cancer comprising melanoma development and occurring.

It would have been *prima facie* obvious at the time the claimed invention was made to use the method to treat the melanoma with cupredoxin. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to use the method to treat a patient with melanoma because application 592' has shown a method of treating patient suffering cancer comprising administering to a patient with a therapeutically effective amount of a cupredoxin, wherein cancer is melanoma and because application 693' has shown method of treating patient suffering angiogenesis comprising administering to a patient with a therapeutically effective amount of a cupredoxin, wherein suffering is melanoma.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a New Ground of rejection-based on amendment to the claims to an in vivo method of treating a patient

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamada et al., (PNAS, vol 99, page 14098-14103, Oct. 2002,).

Claims are amended to drawn to a method of treating a condition related to resisstance to death, comprising administering to a patient an effective amount of cupredoxin comprising azurin, wherein the condition comprisng human melanoma. It is noted that priority for the claim 1, 2 and 20 has been establised as 8/15/2003.

Yamada et al., disclose a method of treating human melanoma comprising administering effecive amount azurin to mice bearing human melanom tumor. Yamada et al., disclose regresion of melanom in nude mice is observed (figure 6-7 and page 14102).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 1-6 and 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, and 7-12 of US patent No. 7084105 in view of Yamada et al., (PNAS, vol 99, page 14098-14103, Oct. 2002, applicant's IDS A23).

Instant amended claims 1-6 and 20 are amended to drawn to a method of treating a condition comprising administering to a patient cupredoxin comprising azurin, and functional variant having 90% of sequence identity to SEQ ID NO:1, wherein azurin binds to tumor-suppressor protein p53 to promote cell death.

Claims 1-3, 5, and 7-13 of US Patent No. 7084105 are drawn to method of treating a cancer comprising melanoma comprising administering to a patient azurin, or truncated azurin, wherein the compound azurin modulate cell death.

Claims US Patent No. 7084105 do not teach azurin binding to p53 to promote cell death,

Yamada et al., disclose azurin binding to tumor suppressor protein p53 and form a complex to induce cell death and regression of cancer (figure 5 and bridge page 14101-2).

It would have been *prima facie* obvious at the time the claimed invention was made to use the method described in claims of US Patent 7084105. One of ordinary skill in the art would have been motivated with reasonable expectation of success to combine the methods to treat a patient with a cancer by promoting cancer cell death by binding to p53 according to the teaching of claims US patent No. 7084105 because the claims of US patent have shown the method of using azurin to treat cancer and Yamada have shown that azurin binds to p53 and regression of cancer. Therefore, the claimed invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention as made, as evidenced by the claims of US Patent 7084105 in combination of Yamada's

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10720603	Applicant(s) Chakrabarty et al	
	Examiner Lei Yao	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: need SEQ ID numbers for sequences in figure 11.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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